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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/081,974 | 02/21/2002 | Joseph Rubinfeld | 12636-263 | 2253 |

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| EXAMINER | |
|---|---|
| FISHER, LATONIA M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1623 | 5 |

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/081,974 | RUBINFELD ET AL. | |
| | Examiner | Art Unit | |
| | La Tonia M. Fisher | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-53 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-53 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 1-53 are pending.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20, 23-47, and 51-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 5-flurouracil, does not reasonably provide enablement for every pyrimidine base analog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 1-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A written description analysis involves three principle factors:

1. Field of the invention and predictability of the art
2. Breadth of the claims
3. For each claimed species/genus, possession of claimed invention at the time of the filing.

The breadth of the claim is such that any pyrimidine analog may be used in the method for treating a disease characterized by the uncontrolled or undesired proliferation of cells. The support in the specification is not adequate for the claim drawn to the treatment of a disease

characterized by the uncontrolled or undesired proliferation of cells (which is interpreted to be cancer) with an analog of pyrimidine. Applicant's intent is to administer multiple active agents. The scope of the chemical compounds encompassed by "pyrimidine analogs" is quite broad, however the disclosure provides a single embodiment, which applicant intends to be sufficient to encompass all "pyrimidine analogs" where no specific analog is distinctly claimed.

The written description requirement for a claimed genus may be satisfied through sufficient description of an adequate representation of species by functional characteristics sufficient to show the applicant was in possession of the claimed genus. There are a variety of analogs to pyrimidine which have diverse and varied anti-cancer effects. Pyrimidine analogs have varied toxicities, limited modes of administration due to oral bioavailability and varied therapeutic efficacies. There is not seen support in the disclosure for combining members of the genus, represented by pyrimidine analogs broadly, with camptothecin as instantly claimed. The compound 5-fluorouracil (5-FU) has absorption problems. The examiner notes there are other pyrimidine analogs for which there is no support seen in the written description. Additional agents are sought to obviate which cost, toxic and the necessity of ambulatory infusion pumps for administration, see Damjanov et al. Oncology, Vol. 14, No. 6. One skilled in this art could not predict the effects many of the pyrimidine analogs used in the treatment of cancer singularly might have when combined with camptothecin. There is not seen art recognized correlative data or specific disclosures in the instant application to provide such broad support for pyrimidine analogs broadly. The claims should be limited to that for which there can be found support in the instant disclosure. There is limited predictability in the art that pyrimidine analogs are capable of treating cancer in combination with an additional anticancer agent as broadly claimed. To

provide adequate support for the breadth of the claims, applicant would have to provide sufficient evidence that an adequate representation of pyrimidine analogs would indeed be efficacious for treating cancer. The data presented shows the treatment of cancer by administration of camptothecin and 5-FU; however, this does not correlate via art recognized evidence or adequate support in the instant disclosure to the treatment of cancer broadly by administering any pyrimidine analog as broadly claimed. An adequate representation of species requires that the species which are expressly described and recognized in the art as representative of the entire genus. What constitutes a "representative number" is an inverse function of the predictability in the art in question. As such, a skilled artisan would not recognize that the compound 5-FU would be adequately representative of pyrimidine analogs for treating cancer broadly. As such, there is not seen any data or correlative prior art evidence which supports applicant's claim that at the time of filing, the application/administration of the compounds of the invention, specifically pyrimidine analogs broadly in combination with camptothecin. The limitation of the pyrimidine analog to 5-FU, and guidance in the claims for pyrimidine co-administration including timing and amounts relative to the additional active agent (in view of the difficulty of administration due to bioavailability issues) might obviate the rejection set forth herein.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20, 23-47, and 51-53 are rejected under 35 U.S.C. 112, second paragraph, because in the absence of the specific analogs to the chemical core claimed (CCC) or distinct language to describe the structural modifications or the chemical name(s) of derivatized (CCC)

of this invention, the identify of said analogs would be difficult to describe or ascertain and the metes and bounds of said analogs Applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

Furthermore, claims 25 and 52 recite the limitation "wherein the cancer is selected from" in the first line of each claim. There is insufficient antecedent basis for this limitation in the claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims1-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubinfeld (USPN 6, 191,119) in view of Achterrath (USPN 6,403,569).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1 is drawn to a method for treating a patient having a disease associated with undesirable or uncontrolled cell proliferation comprising administering to the patient a 20(S)-camptothecin for a period of time during which a pyrimidine base analog is not being administered to the patient and then thereafter administering a pyrimidine base analog to the patient. Further limitations of claim 1 recited in claims 2-26 include the specified period of time the 20(S)-camptothecin is administered before the pyrimidine base analog, the specified period of time the 20(S)-camptothecin is administered after the pyrimidine base analog, the identity of the pyrimidine base analog, the identity of the 20(S)-camptothecin, and the specific disease associated with the undesirable or uncontrolled cell proliferation.

Claim 27 is drawn to a method treating a patient having a disease associated with undesirable or uncontrolled cell proliferation comprising administering to the patient a 20(S)-camptothecin for a period of time during which a pyrimidine base analog is not present in a pharmacologically active form in the patient's body and then thereafter administering a pyrimidine base analog to the patient. Further limitations of claim 1 recited in claims 28-53 include the specified period of time the 20(S)-camptothecin is administered before the pharmacologically active pyrimidine base analog is present in the patient's body, the specified

period of time the 20(S)-camptothecin is administered after the pharmacologically active pyrimidine base analog is present in the patient's body, the identity of the pyrimidine base analog, the identity of the 20(S)-camptothecin, and the specific disease associated with the undesirable or uncontrolled cell proliferation.

Rubinfeld teaches methods for treating a patient having a disease associated with undesirable or uncontrolled cell proliferation comprising administering to the patient a therapeutically effective amount of 20(S)-camptothecins, analogs of 20(S)-camptothecins and derivatives of 20(S)-camptothecins, including 9-ntiro-20(S)-camptothecin. See USPN '119, col. 3, lines 1-5, 35-40 and claims 1-4. Additionally, at column 4, lines 60-62, Rubinfeld teaches the composition according to the prior art invention might include a camptothecin, a non-camptothecin therapeutic agent, together with a pharmaceutical excipient. Rubinfeld discloses that the prior art inventive combination of therapeutic agents and/or compositions may be administered or coadministered orally, parenterally, transdermally, intramuscularly, via local delivery, subcutaneously, etc. See USPN '119, col. 5, lines 45-50. Furthermore, Rubinfeld discloses that coadministration in the context of the prior art invention is defined to mean the administration of more than one therapeutic in the course of a coordinated treatment to achieve an improved clinical outcome; such coadministration may also be coextensive, that is, occurring during overlapping periods of time. See USPN '119, col. 5, lines 54-62. At USPN '119, col. 7, lines 37-40 Rubinfeld also teaches that in certain delivery forms, the appropriate therapeutic agents or composition release times of the prior art invention can vary but preferably should last from about 1 hour to six months. Specific types of cell proliferation disorders taught by the Rubinfeld patent that can be treated using the prior art invention are cancers such as

myelogenous leukemia, bladder, breast, cervical cholangiocarcinoma, colorectal, gastric sarcoma, glioma, lung, lymphoma, melanoma, ovarian, osteosarcomea, pancreatic, prostrate, and stomach cancer.

While Rubinfeld does not specifically teach the use of 5-flurouracil in combination with camptothecin to treat undesirable or uncontrollable cell proliferation, Rubinfeld does suggest combination therapy comprising combining camptothecin analogs and derivatives with non-camptothecin therapeutic agents having therapeutic synergistic effects such as the pyrimidine analogs, 5-fluorouracil and cytarabine in the prior art invention. See USPN '119, col. 2, lines 44-62.

Achterrath teaches methods for treating cancer comprising administering a combination of at least one camptothecin derivative, 5-flurouracil and folinic acid to a host in need thereof. See USPN '569, col. 1, lines 12-15; claim 1.

It would have been obvious for one having ordinary skill in the art at the time the invention was made to administer 20(S)-camptothecin and a pyrimidine base analog such as 5-flurouracil to treat cell proliferation disorders or disease in combination or concurrently, as Applicants have done with the above cited references before them. It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining the compositions and administering same in methods for treating cell proliferation disorders or diseases flows logically from their having been individually taught for said use in prior art. Furthermore, Applicants would have been motivated to combine the art known active agents since Rubinfeld teaches that a synergistic effect is achieved when a greater therapeutic

effect results with a combination therapy than using either drug or monotherapy alone. See USPN '119, col. 4, lines 64-68. It would require little more than routine skill in the art to determine optimum modes and amounts of administration.

***Conclusion***

Claims 1-53 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to La Tonia M. Fisher whose telephone number is (703) 306-5819. The examiner can normally be reached on Monday - Friday from 9:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

LMF
June 14, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
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